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(54) Title: USE OF PRUCALOPRIDE FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DYSPEPSIA

(57) Abstract

The present invention is concerned with the use of prucalopride and pharmaceutically acceptable acid addition salts thereof for the manufacture of a medicament for the treatment of warm–blooded animals, including humans, suffering from dyspeptic symptoms.

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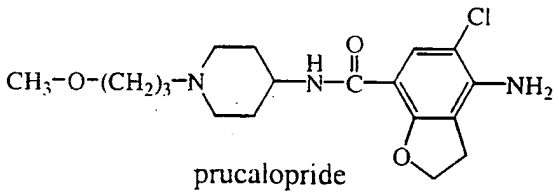
USE OF PRUCALOPRIDE FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DYSPEPSIA

The present invention is concerned with the use of prucalopride and pharmaceutically acceptable acid addition salts thereof for the manufacture of a medicament for the treatment of warm-blooded animals, including humans, suffering from dyspeptic symptoms.

Prucalopride, which is the generic name for the (1:1) succinic acid addition salt of 4-amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofuran-carboxamide, has enterokinetic properties, *i.e.* it has strong gastrointestinal prokinetic activities.



prucalopride

Prucalopride facilitates both cholinergic and non-cholinergic non-adrenergic (NANC) excitatory neurotransmission and stimulates colonic motility and defecation in animals. It has no affinity for 5-HT_{2A} and 5-HT_{3A} receptors but is a potent and selective agonist of 5-HT_4 receptors. Prucalopride induces giant contractions in the colon that are propagated over the length of the colon as a peristaltic wave and therefore has significant motility enhancing effects on the large intestine.

Prucalopride is generically described in EP-0,445,862-A1, published on 11 September 1991, and is specifically disclosed in WO-96/16060, published on 30 May 1996.

The term prucalopride as used herein comprises the free base form and the pharmaceutically acceptable acid addition salts thereof. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, nitric, phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic, salicylic, *p*-aminosalicylic, pamoic and the like acids. The term addition salt as used hereinabove also comprises the solvates which prucalopride as well as the salts thereof, are able to form. Such solvates are for example hydrates, alcoholates and the like.

Preferred pharmaceutically acceptable acid addition salts of 4-amino-5-chloro-2,3-dihydro-*N*-[1-(3-methoxypropyl)-4-piperidinyl]-7-benzofuran-carboxamide are the hydrochloric acid (1:1) addition salt and the succinic acid (1:1) addition salt.

In view of its enterokinetic properties, prucalopride is useful in the treatment of motility disorders of the intestinal system, such as, e.g. constipation, pseudo-obstruction, intestinal atony, post-operative intestinal atony, irritable bowel syndrome (IBS), and drug-induced delayed transit.

Unexpectedly, it was found that prucalopride is also useful to treat patients suffering from dyspeptic symptoms.

Dyspepsia, more commonly known as indigestion, is a very common disorder. In fact, between 15 to 20 percent of the population suffers from it on a recurring basis. Dyspepsia can originate from a number of causes. For instance dyspeptic symptoms can be caused by a disturbed accommodation of food, hypersensitivity either peripherally or centrally mediated, disturbed gastric emptying, disturbed electrical rhythm, disturbed antro-duodenal coordination, or an impaired response to the intraluminal contents.

Recently it is also believed that in a number of patients suffering from dyspepsia, their dyspeptic symptoms may result from a decreased motility of the colon which keeps the colon in a more or less "filled" condition. It is believed that this feeling of a "full" colon or the feeling of pressure exerted on the stomach due to a filled colon can cause an "upset" stomach resulting in a number of dyspeptic symptoms. Said "full" colon may also cause a reflexive inhibition of the stomach resulting in dyspeptic symptoms.

Dyspeptic symptoms are for example a lack of appetite, feeling of fullness, early satiety, nausea, vomiting, bloating and gaseous eructation.

In view of the above described utility of prucalopride, it follows that the present invention also provides a method of treating warm-blooded animals, including humans, (generally called herein patients) suffering from dyspeptic symptoms such as, e.g. a lack of appetite, feeling of fullness, early satiety, nausea, vomiting, bloating and gaseous eructation. Consequently a method of treatment is provided for relieving patients suffering from dyspeptic symptoms, in particular dyspeptic symptoms caused by a

decreased motility of the colon, by administering to said patients a therapeutically effective amount of prucalopride or a pharmaceutically acceptable acid addition salt thereof.

Hence, the present invention provides the use of prucalopride for the manufacture of a medicament for treating dyspeptic symptoms, in particular dyspeptic symptoms caused by a decreased motility of the colon. Both prophylactic and therapeutic treatment are envisaged.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers,

injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

In general it is contemplated that a therapeutically effective amount would be from about 0.001 mg/kg to about 5 mg/kg body weight, preferably from about 0.01 mg/kg to about 0.5 mg/kg body weight. A method of treatment may also include administering the active ingredient on a regimen of between two or four intakes per day.

The amount of prucalopride, or a pharmaceutically acceptable acid addition salt thereof, required as daily dose in treatment will vary not only with the route of administration, the nature of the condition being treated and the age, weight and condition of the patient and will ultimately be at the discretion of the attendant physician. In general, however, a suitable daily dose will be in the range of from about 0.05 to about 200 mg per day, in particular from about 0.1 to 20 mg per day, more particular from about 0.5 to 10 mg per day. A suitable daily dose for use in prophylaxis will generally be in the same range. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Administration can be before or after the intake of food (*i.e.* preprandial or postprandial).

Experimental section.

The efficacy of prucalopride, or a pharmaceutically acceptable acid addition salt thereof, to treat subjects suffering from dyspeptic symptoms can be demonstrated by the following trial.

A group of healthy subjects is treated with an anti-diarrheal compound such as, e.g. loperamide, which causes a mild constipation in said subjects, *i.e.* the normal colon motility is reduced so that the subjects have a colon in a "filled" condition.

The group of subjects is split into a control group and a test group for treatment with prucalopride. The subjects in the test group are then treated with prucalopride.

Then, the subjects in both groups are served a standard breakfast consisting of four slices of bread, one slice of ham, one slice of cheese, butter, jelly and two cups of coffee or tea with, if desired, milk and/or sugar.

The number of subjects suffering from dyspeptic symptoms and the seriousness of the dyspeptic symptoms are recorded and compared between the test group and the control group.

The above described trial can be modified by treating the test group with prucalopride after the subjects have finished their meal. The trial can be done open, or blindfolded, using a randomized group of subjects.

Alternatively, out of a group of subjects suffering from dyspeptic symptoms, a sub-group of subjects can be selected also having reduced colon motility. Said sub-group can be given prucalopride, or a pharmaceutically acceptable acid addition salt thereof, either preprandial or postprandial and the reduction of the number or seriousness of the dyspeptic symptoms can be recorded.

Conversely, out of a group of subjects suffering from reduced colon motility, and therefore having a reduced stool frequency, a sub-group of subjects can be selected also having dyspeptic symptoms. Said sub-group can be given prucalopride, or a pharmaceutically acceptable acid addition salt thereof, either preprandial or postprandial and the reduction of the number or seriousness of the dyspeptic symptoms can be recorded.

Claims

1. Use of prucalopride or a pharmaceutically acceptable addition salt thereof for the manufacture of a medicament for the treatment of patients having dyspeptic symptoms.

2. Use according to claim 1 wherein the dyspeptic symptoms are caused by a decreased motility of the colon.

3. Use according to any of claims 1 to 2 wherein the pharmaceutically acceptable addition salt of prucalopride is the (1:1) succinic acid addition salt.

4. Use according to any of claims 1 to 3 wherein the dyspeptic symptoms comprise lack of appetite.

5. Use according to any of claims 1 to 3 wherein the dyspeptic symptoms comprise the feeling of fullness.

6. Use according to any of claims 1 to 3 wherein the dyspeptic symptoms comprise early satiety.

7. Use according to any of claims 1 to 3 wherein the dyspeptic symptoms comprise nausea and vomiting.

8. Use according to any of claims 1 to 3 wherein the dyspeptic symptoms comprise bloating or gaseous eructation.

9. Use according to any of claims 1 to 3 wherein the daily dose of prucalopride or a pharmaceutically acceptable addition salt thereof ranges from 0.05 mg to 200 mg per day.

10. Use according to claim 9 wherein the daily dose ranges from 0.1 mg to 20 mg per day.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MAT
IPC 7 A61K31/4525 A61K31/445 A61P1/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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